

Applicant : John Edward Norris Morten  
Serial No. : 09/787,371  
Filed : March 16, 2001.  
Page : 2

Attorney's Docket No.:  
06275-277001 / AFG/Z70389-1P US

In the specification:

Please replace the original Sequence Listing with the substitute Sequence Listing, a copy of which is enclosed.

Please replace the paragraph beginning at page 2, line 23 with the following rewritten paragraph:

-- Exon 1 of the VCAM-1 gene has been cloned and published as an EMBL Accession number: M92431 (2396 bp; hereafter referred to as SEQ ID NO:2) and all positions herein relate to the position therein unless stated otherwise or apparent from the context.--

Replace the paragraph beginning at page 3, line 8 with the following rewritten paragraph:

-- According to one aspect of the present invention there is provided a method for the diagnosis of a single nucleotide polymorphism in VCAM-1 in a human, which method comprises determining the sequence of the nucleic acid of the human at one or more of positions 278, 647, 707, 748, 829, and 1467 in the VCAM-1 gene as defined by the positions in SEQ ID NO:2, and determining the status of the human by reference to polymorphism in the VCAM-1 gene.--

Replace the paragraph beginning at page 4, line 7 with the following rewritten paragraph:

--In another aspect of the invention we provide a method for the diagnosis of VCAM-1 ligand-mediated disease, which method comprises:

- i) obtaining sample nucleic acid from an individual,
- ii) detecting the presence or absence of a variant nucleotide at one or more of positions 278, 647, 707, 748, 829, and 1467 (as defined by the position in SEQ ID NO:2), in the VCAM-1 gene, and
- iii) determining the status of the individual by reference to polymorphism in the VCAM-1 gene.--

Replace the paragraph beginning at page 6, line 23 with the following rewritten paragraph:

-- In a further aspect, the diagnostic methods of the invention are used to assess the efficacy of therapeutic compounds in the treatment of VCAM-1 ligand mediated diseases such as autoimmune, allergic and vascular inflammatory diseases. The polymorphisms identified in the present invention occur in the promoter region of the VCAM-1 gene. The changes are not expected to alter the amino acid sequence of VCAM-1, but several of the polymorphisms affect transcription sites within the promoter region and thus may affect the transcription of the VCAM-1 gene. For example the changing of the nucleotide at position 748 (as defined by the position in SEQ ID NO:2) from T to C results in the gain of an E1a-F rev site and the loss of a TATA box.--

Replace the paragraph beginning at page 7, line 27 with the following rewritten paragraph:

-- According to another aspect of the present invention there is provided a nucleic acid comprising any one of the following polymorphisms:  
the nucleic acid of SEQ ID NO:2 with C at position 278 in the promoter sequence;  
the nucleic acid of SEQ ID NO:2 with G at position 647 in the promoter sequence;  
the nucleic acid of SEQ ID NO:2 with C at position 707 in the promoter sequence;  
the nucleic acid of SEQ ID NO:2 with C at position 748 in the promoter sequence;  
the nucleic acid of SEQ ID NO:2 with A at position 829 in the promoter sequence;  
the nucleic acid of SEQ ID NO:2 with C at position 1467 in the promoter sequence;  
or a complementary strand thereof or a fragment thereof of at least 20 bases comprising at least one polymorphism.--

Replace the paragraph beginning at page 10, line 18 with the following rewritten paragraph:

-- According to another aspect of the present invention there is provided an allele specific primer capable of detecting a VCAM-1 gene polymorphism at one or more of positions 278, 647, 707, 748, 829 and 1467 in the VCAM-1 gene as defined by the positions in SEQ ID NO:2.--

Replace the paragraph beginning at page 11, line 6 with the following rewritten paragraph:

-- According to another aspect of the present invention there is provided an allele-specific oligonucleotide probe capable of detecting a VCAM-1 gene polymorphism at one or more of positions 278, 647, 707, 748, 829, and 1467 in the VCAM-1 gene as defined by the positions in SEQ ID NO:2.--

Replace the paragraph beginning at page 11, line 25 with the following rewritten paragraph:

-- In another aspect of the invention, the single nucleotide polymorphisms of this invention may be used as genetic markers in linkage studies. This particularly applies to the polymorphism at 278 (as defined by the position in SEQ ID NO:2) because of its relatively high frequency (see below). The VCAM-1 gene has been mapped to chromosome 1p31-32 (Cybulsky et al Proc. Natl. Acad. Sci. USA **88**, 7859-7863, 1991).--

Replace the paragraph beginning at page 12, line 16 with the following rewritten paragraph:

--According to another aspect of the present invention there is provided a method of treating a human in need of treatment with a VCAM-1 ligand antagonist drug in which the method comprises:

- i) diagnosis of a single nucleotide polymorphism in VCAM-1 gene in the human, which diagnosis comprises determining the sequence of the nucleic acid at one or more of positions 278, 647, 707, 748, 829, and 1467 (as defined by the position in SEQ ID NO:2), and determining the status of the human by reference to polymorphism in the VCAM-1 gene; and
- ii) administering an effective amount of a VCAM-1 ligand antagonist.--

Replace the paragraph beginning at page 13, line 4 with the following rewritten paragraph:

--According to another aspect of the present invention there is provided use of a VCAM-1 ligand antagonist drug in preparation of a medicament for treating a VCAM-1 ligand

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mediated disease in a human diagnosed as having a single nucleotide polymorphism at one or more of positions 278, 647, 707, 748, 829, and 1467 (as defined by the position in SEQ ID NO:2).--

Replace the paragraph beginning at page 13, line 9 with the following rewritten paragraph:

--According to another aspect of the present invention there is provided a pharmaceutical pack comprising VCAM-1 ligand antagonist drug and instructions for administration of the drug to humans diagnostically tested for a single nucleotide polymorphism at one or more of positions 278, 647, 707, 748, 829, and 1467 (as defined by the position in SEQ ID NO:2).--

Replace the sentence beginning at page 15, line 1 (in the Table legend) with the following rewritten sentence:

-- <sup>1</sup>As defined by the position in SEQ ID NO:2--

Replace the paragraph beginning at page 15, line 9 with the following rewritten paragraph:

-- Standard methodology can be used to detect the polymorphism at position 647 (as defined by the position in SEQ ID NO:2) based on the materials set out below.--

In the claims:

Please amend claim 1 as follows:

--1. (Amended) An assay for detecting a nucleotide polymorphism in the human VCAM-1 gene, which method comprises determining the sequence at one or more of positions 278, 647, 707, 748, 829, and 1467 in the VCAM-1 gene as defined by the positions in SEQ ID NO:2.--

Amend claim 4 as follows:

--4. (Amended) An isolated and purified nucleic acid comprising any one of the following polymorphisms: